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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

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PCT/GB98/01722

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HMJ03113WO

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12 June 1998 (12.06.98)

Priority date (day/month/year)

Applicant

JONES, Richard, Henry et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

27 December 1999 (27.12.99)

☐ in a notice effecting later election filed with the International Bureau on:

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Juan Cruz

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TENT COOPERATION TRE Y

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NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

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Broadgate House
7 Eldon Street
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ROYAUME-UNI

Date of mailing (day/month/year) 18 January 2000 (18.01.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference HMJ03113WO	
International application No. PCT/GB98/01722	International filing date (day/month/year) 12 June 1998 (12.06.98)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

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☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

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(71) Applicants (for all designated States except US): KINGS COLLEGE LONDON [GB/GB]; Strand, London WC2R 2LS (GB). DEUTSCHES WOLFFORSCHUNGSINSTITUT [DE/DE]; Veltmanplatz 8, D-5100 Aachen (DE).			
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(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).			
(54) Title: INSULIN ANALOGUE			
(57) Abstract			
A novel analogue of insulin has covalently conjugated thereto, preferably at the B1 residue, 3,3',5'-triiodothyroxine. The conjugate is believed to be hepatoselective, whilst it retains insulin receptor binding properties.			

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INSULIN ANALOGUE

The present invention relates to novel insulin analogues which are covalent conjugates of an insulin molecule and a derivative of the hormone thyroxine, 3,3',5'triiodothyronine.

In WO-A-95/05187 we described novel insulin conjugates with hormones, specifically with tetraiodothyroxine (3,3',5,5'tetraiodothyronine, T4), which were hepatoselective. The hepatoselectivity was believed to be due to the fact that, when introduced percutaneously, the size of the molecule (about 15% higher molecular weight than insulin itself) allows it to diffuse through the capillary endothelium into the circulation. In the circulation it is believed to bind reversibly the circulating proteins having an affinity for the thyroxine moiety, namely thyroxine binding globulin, thyroxine binding prealbumin and albumin, collectively known as thyroxine binding proteins (TBP). These higher molecular weight complexes are then unable to diffuse back through capillary endothelium, but are able to diffuse through the relatively larger pores of the hepatic endothelium. The conjugate is found to retain insulin activity. The hepatoselectivity ensures that insulin is directed to the site where its activity is required.

In WO-A-95/07931 hydrophobically modified insulin analogues are described. The insulin is generally derivatised by acylation of the pendant amino group of lysine at B29 with a fatty acid. However there is also an example of derivatising that residue with thyroxine, or with tetraiodothyroacetic acid. The analogues are alleged to have a protracted profile of action, although the mechanism by which this takes place is not elucidated.

One potential problem with the T4-insulin conjugate is that it may retain thyroxine activity. The present invention seeks to solve this problem while providing a conjugate which retains its hepatoselectivity, insulin activity and circulating protein affinity.

A new compound according to the invention comprises an insulin molecule covalently bound to 3,3',5'-triiodothyronine.

The 3,3',5'-triiodothyronine molecule is not a naturally occurring compound. It is an isomer of 3,5,3'-triiodothyronine (T3) and is consequently known as reverse T3, rT3. It has insignificant activity on thyroxine receptor, but thyroxine binding proteins have an affinity for the molecule. Thus the compound of the invention should have affinity for TBP's and, it is believed, consequential hepatoselectivity whilst the compound and its metabolites should not stimulate thyroxine activity.

The rT3 moiety should be conjugated to a residue of the insulin molecule such that insulin activity is not adversely affected. As in WO-A-95/05187, conjugation is preferably through the B1 residue of insulin. Alternatively the B29 residue may be linked to rT3. In WO-95/07931, the B29 residue may be derivatised and the methods of conjugating a carboxylic acid-containing compound to the B29 residue as disclosed in that reference may be used in the present invention.

The insulin may be made by recombinant DNA techniques or may be isolated from natural sources, human or animal. Recombinant insulin may have deleted residues as desired, for instance the B29 residue may be deleted. Other residues of naturally occurring insulin may be substituted, usually by conservative substitutions. For instance in WO-A-95/07931, analogues in which the B3 and/or A21 residues are other than those of naturally occurring insulin.

The rT3 molecule is conjugated to the insulin using conventional biochemical techniques in which pendant groups on the appropriate residue of the insulin molecule are covalently bonded to rT3, through the carboxylate group. The pendant group is usually the ϵ -amino group of a lysine residue. Any other lysine residues may be rendered unreactive by protecting the ϵ -amine groups using

conventional techniques. Protecting groups are removed after conjugation to the rT3 molecule.

The phenolic OH group of rT3 is protected during the process, also.

5 Either or both of the amine group and the carboxylate group may be activated prior to contact of the insulin with the rT3. Conventional techniques for generation of amide linkages may be used, for instance using known reagents.

10 A spacer may be included between the insulin molecule and the rT3 molecule. A spacer may, for instance, improve retention of insulin activity and/or TBP-binding. A spacer may also be used to control *in vivo* cleavage and metabolism of the conjugate compound, and consequently its insulin activity. A spacer may, for instance include a chain
15 comprising 2 to 22 carbon and/or heteroatoms, such as a 4-10 atom chain, preferably comprising an alkylene group and carbonyl and/or amino groups, amido groups and or oxygen atoms in ester or ether linkages.

20 The inventors have found that the insulin-rT3 conjugate has a similar potency relative to human insulin itself. This is in contrast to T4-insulin, which appears to have a greater potency than human insulin. In the presence of binding proteins, especially thyroxin binding proteins, the potency of T4-insulin is reduced, whereas
25 these proteins do not affect the potency of rT3-insulin. These data indicate that the conjugate is likely to have similar effects as insulin *in vivo*.

30 Further tests in which the ED50 of the conjugates as compared to insulin, in the presence and absence of binding proteins (human serum albumin and thyroxin binding globulin and transthyretin) show that each conjugate on its own has a similar ED50 to human insulin itself. The ED50's of the T4-insulin conjugate are significantly increased by the presence of TBG, whilst the ED50's of the rT3-insulin are
35 not effected to a significant degree.

We have also conducted competitive binding assays of the insulin analogues compared to human insulin with

¹²⁵-Insulin to insulin receptors on liver plasma membrane (LPM). Insulin is known to inhibit the binding of ¹²⁵-Insulin to these receptors. We have found that TBP does not affect this ability. rT3 behaves in a similar way to human insulin in that it inhibits binding of ¹²⁵-Insulin to the receptors on LPM and this is not affected by the presence of TBP. T4 insulin itself does inhibit ¹²⁵-Insulin binding to these receptors. In contrast, however, TBP significantly affects this inhibition.

The novel compound is suitable for use in a method of treatment of the human or animal, for instance to replace insulin in a method of insulin replacement therapy. The invention thus comprehends novel compositions containing the compound as well as pharmaceutical compositions containing the compound and a pharmaceutically acceptable excipient. The composition is formulated so as to be suitable for administration by the usual routes, generally by subcutaneous injection. Accordingly the carrier is generally aqueous. The invention comprehends also a new use of the compound in the manufacture of a medicament for use in a method of treatment of the human or animal body.

The following examples illustrate the invention.

25

Example 1Preparation of [rT3(Na-B1)]-insulin1.1 Synthesis of Msc-rT3

30

50.0 mg rT3	(76.8 umol, 651.0 g/mol)
20.4 mg Msc-OSu	(76.9 umol, 265.24 g/mol)

35

50.0 mg rT3 were suspended in 400 ul dimethylformamide and 20.4 mg Msc-OSu, dissolved in 100 ul dimethylformamide, were added. 4 ul of triethylamine were pipetted into the solution and the mixture was stirred overnight at room temperature.

1.2 Synthesis of Msc-rT3-OSu

16.6 mg DCC (80.6 μmol , 206.3 g/mol)

16.6 μmol DCC were dissolved in 50 μl dimethylformamide
5 and added to the above reaction mixture. The activation is
complete after 3 h at room temperature.

1.3 Synthesis of [rT3(Na-B1)]-insulin

10 230 mg A1,B29-(Msc)2-insulin (6078 g/mol, 38 μmol)
synthesised according to Schüttler A and Brandenburg D,
Hoppe-Seyler's Z. Physiol.Chem. 360, 1721-1725 (1979) were
dissolved in 3 ml dimethylformamide with the addition of 4
15 μl triethylamine and then reacted with 69 μg Msc-rT3-OSu
(898 g/mol, 76 μmol , two-fold excess with respect to
insulin derivative). After stirring for 3 h at room
temperature the acylation was stopped by addition of 50 μl
acetic acid. The solution was dialysed overnight against
distilled water and lyophilised. For cleavage of Msc
20 protecting groups the protein material was diluted in a
mixture of 1 ml dimethylformamide, 1.5 ml methanol and 1.5
ml water. The solution was cooled to 0°C and addition of
0.5 ml of ice-cold 2 M sodium hydroxide solution started
the cleavage reaction. The reaction was stopped by
25 acidification with 1 ml of 10% (v/v) acetic acid. The
protein was precipitated by pipetting the reaction solution
into a mixture of 250 ml of ice-cold ether and 20 ml
methanol and stirring for 1 h. The ether was decanted
from the precipitated protein and the protein dried in
30 vacuo.

Purification of the raw material was performed by use
of RP-MPLC. Fractions were collected and lyophilised.
Chromatographic conditions:

Column: RP20C18, 2.5 x 250 mm, 122 ml total volume,
35 Gradient: 25-40% (v/v)
2-propanol in water containing 0.1% trifluoro acetic
acid, total gradient volume 1.5 l; flow rate 20 ml / 3 min.

Yield: 27 mg (10% of theory, based on A1,B29-(Msc)2-insulin)

Molecular mass: 6437 u (calc. 6436.6 u)

Purity (RP-HPLC): 93 % (Absorption at 215 nm)

5

1.4 Mass spectrometry

MS-TOF spectrometer VG ToFSpec, Fisons

Ionisation: Ar-laser, MCP Volts, : 1750, 337 nm, linear
modus Acceleration: 20 kV

10 Standard: bovine insulin 5731 u (calc. 5731 u),
vasointestinal peptide 1424 u (calc. 1426 u) [rT3(Na-B1)]-
insulin: 6437 (calc. 6437)

Example 2 - Effects of Binding Proteins on Receptor

15 Binding

The rT3-insulin conjugate made in Example 1 is used in various tests to determine the binding potencies of the analogues on liver plasma membrane. ¹²⁵-Insulin is used as
20 the labelled insulin. It is known that insulin itself inhibits binding of ¹²⁵-Insulin.

Results

Equilibrium binding curves

25 The equilibrium binding curves of average normalised bound against the log-concentration of insulin or analogue (nmol/l) with or without the presence of THBP were generated. The trends initially illustrated by the curves were:

30 H-Ins, rT3-Ins and T4-Ins appear similar in their positions, i.e. there is no difference between them in their ability to inhibit the binding of ¹²⁵-Insulin to insulin receptors on LPM.

35 The presence of THBP does not appear to affect the ability of H-Ins to inhibit the binding of ¹²⁵-Insulin to insulin receptors on LPM.

The presence of THBP does not appear to affect the ability of rT3-Ins to inhibit the binding of 125 -Insulin to insulin receptors on LPM.

5 The presence of THBP does appear to affect the ability of T4-Ins to inhibit the binding of 125 -Insulin to insulin receptors on LPM as shown by the shift in the T4-Ins+THBP curves to the right. TBG seems to have the greatest effect on T4-Ins, i.e. causes the greatest shift.

ED50

10 The ED50's as calculated by the G-PIP software were inverse logged because the concentrations entered in G-PIP had to be entered as the log of the concentrations. The average (nmol/l) \pm SEM of the ED50's was then calculated. The results are shown in Table 1. These give a
15 quantitative idea of the shift, if any in the equilibrium binding curves.

TABLE 1

Average of ED50 \pm SEM			
	Average	SEM	n=
20 H-Ins	1.966	0.43	5
rT3-Ins	2.455	0.35	6
0.5% HSA	2.48	0.478	4
1% HSA	3.24	0.379	3
25 2.5% HSA	2.76		2
Transthyretin	1.805	0.55	4
0.135 μ mol/l TBG	3.147	0.35	3
T4-Ins	1.316	.034	5
0.5% HSA*	3.715		2
30 1% HSA*	5.823	2.108	3
2.5% HSA*	4.81		2
Transthyretin*	2.935	0.32	4
0.135 μ mol/l TBG*	21.67	2.258	3
0.27 μ mol/l TBG*	36.55		2

* Fisher's test also performed.

Statistical analysis of the ED50's

From the statistical analysis it was found that the
5 ED50's of rT3-Ins and T4-Ins were not significantly
different from that of H-Ins. The ED50's of rT3-Ins with
THBP were not significantly different from those of rT3-Ins
without THBP present as determined by ANOVA. On the other
hand, the ED50's of T4-Ins without THBP present ($p < 0.05$) as
10 determined by Fisher's least squares test (see Table 1*).

Potency estimates

The potency estimates of the analogues relative to H-
Ins and the analogues in the presence of THBP relative to
15 the analogues in the absence of THBP are shown in Table 2
with their fiducial limits. This demonstrates that rT3-Ins
has a similar potency relative to H-Ins. T4-Ins seems to
have a greater potency relative to H-Ins. The presence of
THBP seems to have no effect on the binding potency
20 estimates of rT3-Ins binding to insulin receptors relative
to rT3-Ins without THBP present. However the presence of
THBP present. However the presence of THBP greatly reduces
the T4-Ins binding potency estimates relative to T4-Ins
binding to insulin receptors without THBP present (Table
25 2).

TABLE 2

Potency Estimates		
	Potency	95% fiducial limits
5	H-Ins	100%
	rT3-Ins	94%
	T4-Ins	184%
10	rT3-Ins	100%
	0.5% HSA	122%
	1% HSA	87%
	2.5% HSA	119%
	0.135 μ mol/l TBG	76%
	Transthyretin	183%
15	T4-Ins	100%
	0.5% HSA	27%
	1% HSA	31%
	2.5% HSA	35%
	0.135 μ mol/l TBG	5%
	Transthyretin	33%
20		

Scatchard Plots

The Scatchard plot of H-Ins demonstrates the characteristic curvilinear shape of negative co-operativity that should be exhibited by human insulin. It may be seen from the Scatchard plots of rT3-Ins and T4-Ins that these analogues also exhibit negative co-operativity due to their curvilinear shape.

Reference Example - Synthesis of Insulin - T4

The T4 insulin is B1-thyroxyl-insulin made according to the technique described in WO-A-95/05187, Example 1.

CLAIMS

1. A compound consisting of an insulin molecule covalently bound to 3,3',5' triiodothyromine.

2. A compound according to claim 1 in which the
5 3,3',5' triiodothyromine is bound to a lysine residue of the insulin molecule.

3. A compound according to claim 2 in which the 3,3',5' triiodothyromine is bound to the B1 lysine residue.

4. A compound according to any preceding claim in
10 which the insulin is human insulin.

5. A compound according to any preceding claim for use in a method of treatment of the human or animal body.

6. A composition comprising a compound according to any of claims 1 to 4 and a carrier.

15 7. A pharmaceutical composition comprising a compound according to any of claims 1 to 4 and a pharmaceutically acceptable excipient.

8. Use of a compound according to any of claims 1 to 4 in the manufacture of a composition for use in a method
20 of treatment of the human or animal body.

9. Use according to claim 8 in which the method is insulin replacement therapy, preferably for treatment of diabetes.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/01722

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/62 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 05187 A (UNITED MEDICAL & DENTAL SCHOOL ; DEUTSCHES WOLFFORSCHINST (DE)) 23 February 1995 cited in the application see abstract	1-8
A	WO 95 07931 A (NOVO NORDISK) 23 March 1995 cited in the application see abstract see examples	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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WO 9505187 A	23-02-1995	EP 0725648 A	14-08-1996
		JP 10501789 T	17-02-1998
		US 5854208 A	29-12-1998

WO 9507931 A	23-03-1995	AU 4846197 A	19-02-1998
		AU 682061 B	18-09-1997
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		NO 961070 A	15-05-1996
		NZ 273285 A	24-10-1997
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HMJ03113WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB98/01722International filing date (day/month/year)
12/06/1998Priority date (day/month/year)
12/06/1998Applicant
KINGS COLLEGE LONDON

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HMJ03113WO		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB98/01722	International filing date (day/month/year) 12/06/1998	Priority date (day/month/year) 12/06/1998	
International Patent Classification (IPC) or national classification and IPC C07K14/62			
Applicant KINGS COLLEGE LONDON			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 4 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 			
Date of submission of the demand 27/12/1999		Date of completion of this report 28.06.00	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Halle, F Telephone No. +49 89 2399 8537	



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB98/01722

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

Description, pages:

1-9 as originally filed

Claims, No.:

1-9 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB98/01722

2. Citations and explanations

see separate sheet

Section V

Having regard to the prior art, the subject-matter of claim 1-9 appears to be novel (Article 33(2) PCT). The prior art documents WO-A-95 05187 and WO-A-95 07931 (both cited in the application), which are considered to represent the most relevant state of the art, disclose insulin analogues which are covalent conjugates of an insulin molecule and a covalently bound thyroxine-derived molecule. A technical problem by using thyroxine-derived molecules is that the insulin conjugate may retain thyroxine activity. This problem appears to be solved by the present invention by using a covalent insulin conjugate wherein the thyroxine-derived molecule is 3,3',5'-triiodothyronine; the cited prior art does not refer to such an insulin conjugate.

The subject-matter of claims 1-9 also appears to involve an inventive step (Article 33(3) PCT). Since the problem with the remaining thyroxine activity has been solved, the proposed invention is not only an alternative covalent insulin conjugate but also an advantageous conjugate solving the problem of thyroxine activity while retaining in particular its insulin activity. Since no indication has been made in the prior art to obtain such an advantageous insulin conjugate, the claimed invention is not obvious to a person skilled in the art.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference HMJ03113W0	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 98/ 01722	International filing date (day/month/year) 12/06/1998	(Earliest) Priority Date (day/month/year)
Applicant KINGS COLLEGE LONDON		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ **Certain claims were found unsearchable** (see Box I).
2. ☐ **Unity of invention is lacking** (see Box II).
3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
 - ☐ filed with the international application.
 - ☐ furnished by the applicant separately from the international application.
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ Transcribed by this Authority
4. With regard to the **title**, ☒ the text is approved as submitted by the applicant
 - ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract**, ☒ the text is approved as submitted by the applicant
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the **drawings** to be published with the abstract is:
 - Figure No. ☐ as suggested by the applicant. ☐ None of the figures.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/01722

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/62 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 05187 A (UNITED MEDICAL & DENTAL SCHOOL ; DEUTSCHES WOLFFORSCHINST (DE)) 23 February 1995 cited in the application see abstract ---	1-8
A	WO 95 07931 A (NOVO NORDISK) 23 March 1995 cited in the application see abstract see examples -----	1-8

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

2 February 1999

Date of mailing of the international search report

10/02/1999

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Panzica, G

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/01722

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9505187 A	23-02-1995	EP 0725648 A	14-08-1996
		JP 10501789 T	17-02-1998
		US 5854208 A	29-12-1998
WO 9507931 A	23-03-1995	AU 4846197 A	19-02-1998
		AU 682061 B	18-09-1997
		AU 7652094 A	03-04-1995
		BG 61611 B	30-01-1998
		BG 100420 A	31-12-1996
		BR 9407508 A	07-01-1997
		CA 2171424 A	23-03-1995
		CN 1133598 A	16-10-1996
		CZ 9600789 A	16-10-1996
		EP 0792290 A	03-09-1997
		FI 961220 A	14-05-1996
		HU 75991 A	28-05-1997
		JP 9502867 T	25-03-1997
		NO 961070 A	15-05-1996
		NZ 273285 A	24-10-1997
		PL 313444 A	08-07-1996
		SK 32496 A	06-11-1996
		US 5750497 A	12-05-1998
		ZA 9407187 A	17-03-1995